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Real-Time 3D Echo in Patient Selection for Cardiac Resynchronization Therapy

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OBJECTIVES This study investigated the use of 3-dimensional (3D) echo in quantifying left ventricular mechanical dyssynchrony (LVMD), its interhospital agreement, and potential impact on patient selection.

BACKGROUND Assessment of LVMD has been proposed as an improvement on conventional criteria in selecting patients for cardiac resynchronization therapy (CRT). Three-dimensional echo offers a reproducible assessment of left ventricular (LV) structure, function, and LVMD and may be useful in selecting patients for this intervention.

METHODS We studied 187 patients at 2 institutions. Three-dimensional data from baseline and longest follow-up were quantified for volume, left ventricular ejection fraction (LVEF), and systolic dyssynchrony index (SDI). New York Heart Association (NYHA) functional class was assessed independently. Several outcomes from CRT were considered: 1) reduction in NYHA functional class; 2) 20% relative increase in LVEF; and 3) 15% reduction in LV end-systolic volume. Sixty-two cases were shared between institutions to analyze interhospital agreement.

RESULTS There was excellent interhospital agreement for 3D–derived LV end-diastolic and end- systolic volumes, EF, and SDI (variability: 2.9%, 1%, 7.1%, and 7.6%, respectively). Reduction in NYHA functional class was found in 78.9% of patients. Relative improvement in LVEF of 20% was found in 68% of patients, but significant reduction in LV end-systolic volume was found in only 41.5%. The QRS duration was not predictive of any of the measures of outcome (area under the curve [AUC]: 0.52, 0.58, and 0.57 for NYHA functional class, LVEF, and LV end-systolic volume), whereas SDI was highly predictive of improvement in these parameters (AUC: 0.79, 0.86, and 0.66, respectively). For patients not fulfilling traditional selection criteria (atrial fibrillation, QRS duration <120 ms, or undergoing device upgrade), SDI had similar predictive value. A cutoff of 10.4% for SDI was found to have the highest accuracy for predicting improvement following CRT.

CONCLUSIONS The LVMD quantification by 3D echo is reproducible between centers. SDI was an excellent predictor of response to CRT in this selected patient cohort and may be valuable in identifying a target population for CRT irrespective of QRS morphology and duration. (J Am Coll Cardiol Img 2011; 4:16–26) © 2011 by the American College of Cardiology Foundation

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Cardiac resynchronization therapy (CRT) has emerged as an important therapeutic intervention in the treatment of chronic heart failure. In multicenter trials, selected patients with chronic heart failure undergoing CRT experience significant improvement in both markers of subjective well-being and echo parameters of cardiac function as well as clinical end points such as hospitalization for heart failure and death (1–6). Selection criteria in trials of CRT have been relatively uniform in identifying patients with symptomatic chronic heart failure (New York Heart Association [NYHA] functional class III or IV on optimal medical therapy, left ventricular ejection fraction [LVEF] ≤35%) and electrocardiographic (ECG) evidence of dyssynchronous LV contraction (prolonged QRS duration [QRSd] with left bundle branch block [LBBB] pattern on surface ECG) (7–9). These widely accepted patient selection criteria are, however, associated with a 20% to 30% nonresponder rate.

Nonresponse to CRT may reflect intrinsic characteristics of the heart (i.e., synchrony cannot be improved) or inadequacies in conventional CRT methods (i.e., synchrony does not improve because of inability to pace at an appropriate location with current technology). In attempting to identify potential responders to CRT more accurately, studies examining various imaging modalities have suggested that there is a correlation between presence of significant left ventricular mechanical dyssynchrony (LVMD) and positive outcome from CRT. Several echocardiographic methods in particular have appeared promising in a large number of single-center trials. However, a lack of reproducibility in multicenter trials has cast some doubt over the clinical applicability of these techniques (10–12). Real-time 3-dimensional echocardiography (RT3DE) has been proposed as an alternative and potentially more accurate method for quantifying LVMD and identifying patients suitable for CRT (13). Several studies have proven this modality to be the most accurate echocardiographic method for quantifying LV volumes and function (14–21), which in itself may have an important impact on clinical practice (22).

We previously demonstrated that RT3DE can be used to examine and quantify endocardial motion of all myocardial segments across their entire surface. This has allowed us to derive a potentially more accurate measure of LVMD called the systolic dyssynchrony index (SDI) (13), which has been reproduced in multiple later studies (23–30). In this 2-center study, we investigate in potential value of RT3DE in patients undergoing CRT, intercenter variability in quantification, and the ability of the technique to identify responders to this therapy.

METHODS

We investigated 187 patients undergoing primary implant or upgrade to biventricular pacemakers or defibrillators between 2004 and 2008 at King's College Hospital (KCH), London, United Kingdom and the Prince of Wales Hospital, Chinese University of Hong Kong (CUHK), Hong Kong, China. Data from 62 cases were shared across sites for interhospital variability assessment. Clinical and echocardiographic outcomes were recorded at baseline and longest follow-up.

Patient selection. Patient selection for CRT was guided by traditional criteria: normal sinus rhythm with LVEF ≤35%, symptomatic heart failure (NYHA functional class III/IV) on maximal achievable medical therapy, and QRS prolongation (≥120 ms) with LBBB pattern on ECG. At the implanter's discretion, patients not fulfilling all these criteria were also considered for biventricular pacing, thus including some patients with right bundle branch block, paced rhythm, QRSd <120 ms, or persistent atrial fibrillation. In these patients, baseline echocardiographic assessment of LVMD was also taken into account.

Clinical assessment. All patients were regularly reviewed by nurse specialists in heart failure. Functional capacity was assessed according to the NYHA functional classification. NYHA functional class was assigned before implantation and at each subsequent visit, without reference to echo findings. Clinical information was retrieved at the end of the observation period.

Echocardiography. RT3DE studies were performed with the Sonos 7500 or iE33 systems (Philips Medical Systems, Andover, Massachusetts). Three-dimensional datasets were acquired in the apical window with an ECG-gated acquisition as previously described (13). In patients with arrhythmia, including atrial fibrillation, multiple acquisitions were performed until a dataset with no appreciable translation artifacts could be obtained, as we previously described (13).

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve
CRT = cardiac resynchronization therapy
ECG = electrocardiography
ICC = intraclass correlation coefficient
LBBB = left bundle branch block
LVEF = left ventricular ejection fraction
LVESV = left ventricular end-systolic volume
LVMD = left ventricular mechanical dyssynchrony
NYHA = New York Heart Association
QRSd = QRS duration
ROC = receiver-operator characteristic
RT3DE = real-time 3-dimensional echocardiography
SDI = systolic dyssynchrony index

Quantification of dyssynchrony. RT3DE acquisitions were analyzed with 4-dimensional LV analysis (Research Arena 2.0, TomTec, Munich, Delaware). This software is performs 3D endocardial border tracking throughout the cardiac cycle, to provide a mathematical model of the LV volume. This is segmented into 16 subvolumes corresponding to the standard myocardial segments to derive time-volume curves for each. Time to peak contraction (minimum volume) in each segment is normalized for the R-R duration, and SDI is defined as the standard deviation of these timings, expressed as a percentage of cardiac cycle duration.

Device optimization. Atrioventricular delay was adjusted 2 ± 1 day after implantation by examination of LV inflow with pulsed Doppler at the mitral position. The average atrioventricular delay was 115 ± 15 ms. All patients received synchronous biventricular pacing as default after implantation and no adjustment of the interventricular delay was performed before discharge.

Outcomes. Several outcomes were taken as positive response to CRT. A reduction in NYHA functional class by at least 1 class was considered a positive clinical response. A relative increase in LVEF by 20% was considered a positive echocardiographic response. Reverse remodeling was defined as at least 15% reduction in LV end-systolic volume (LVESV). Empirically, patients often report subjective improvement despite not reaching these thresholds. A more sensitive measure of outcome—≥10% relative increase in LVEF—was therefore also included on an exploratory basis, though this approaches the limit of reproducibility of the technique.

Interhospital variability. Three-dimensional echo has been shown to be highly reproducible in single-center studies (13,23,26,27,30). To assess variability between centers, 62 datasets were shared between the 2 participating specialist cardiology centers. To ensure that methodology was comparable, investigators at CUHK underwent 1 week of intensive training with an experienced operator from KCH prior to the study. For this purpose, 20 datasets with a variety of pathologies were analyzed, and at the end of the training period there was excellent agreement. The datasets—43 from KCH and 19 from CUHK—were analyzed independently at both sites to examine interhospital variability of end-diastolic and end-systolic volumes, LVEF, and SDI. To illustrate the impact of image quality of measurement variability, we assessed this based on number of missing segments, endocardial definition, and presence of artifacts; datasets were qualitatively assessed as excellent, average, or poor.

Statistics. Continuous variables are expressed as mean ± SD and compared with parametric (analysis of variance) and nonparametric (Wilcoxon signed rank and Kruskal-Wallis) tests. Nominal variables are expressed as absolute count and percentages and compared with the chi-square or Fisher exact tests. Correlations were assessed with linear and polynomial regression.

Outcomes were assessed with logistic regression to create receiver-operator characteristic (ROC) and calculate probability of response for each level of SDI and QRS. Optimal cutoffs were selected as the level with the highest (sensitivity − [1 − specificity]).

Odds ratios were derived by dichotomous analysis based on traditional values for QRSd (120 ms) and the observed best cutoff for SDI (10.4%).

Interobserver agreement was assessed with intraclass correlation coefficient (ICC), linear regression, and Bland-Altman plots; variability was expressed as mean difference of measurements as well as adjusted for the mean of each pair of measurements. JMP version 7 (SAS Institute Inc., Cary, North Carolina) and PASW Statistics version 18 (SPSS Inc., Chicago, Illinois) were used for statistical analyses.

RESULTS

During the period from 2004 to 2008, 187 patients at KCH and CUHK, underwent primary implantation of, or upgrade to, biventricular pacing. Twenty-one patients (11.2%) were excluded due to limited image quality or rhythm disturbances preventing acquisition of analyzable 3D datasets. Baseline and follow-up data were available for 147 patients with 19 patients lost to follow-up. There were 116 (78.9%) men, and 103 (70%) patients had ischemic heart disease. The time to longest follow-up echo was 7 ± 3 months (median follow-up 6 months, shortest follow-up 2 months). The 2 cohorts had similar baseline QRSd (137 ± 23 ms vs. 128 ± 30 ms for KCH and CHUK, respectively, $p = 0.15$) but differed in baseline NYHA functional class (KCH patients in NYHA functional class II = 9 [6.1%] vs. 9 [50%] for CHUK, chi-square $p < 0.001$) and LVEF (21.5 ± 7.3% vs. 27.6 ± 7.3%, respectively, $p = 0.0012$). Patients lost to follow-up had similar baseline characteristics (QRSd: 131 ± 18, $p = 0.18$, LVEF: 24 ± 9.1%, $p = 0.7$). Baseline clinical and echo characteristics are shown in Table 1.

Table 1. Baseline Characteristics for Patients Included in the Study (n = 166)

NYHA functional class	3.0 ± 0.5
Male sex	131 (78.9%)
Age (yrs)	66.4 ± 12.0
Ischemic LVD	116 (70.1%)
LBBB	112 (67.4%)
QRS duration (ms)	136.7 ± 22.0
QRS ≥120 ms	138 (83%)
Atrial fibrillation	32 (19%)
LVEDV	206.1 ± 73.8
LVESV	164.6 ± 64.6
LVEF (%)	21.5 ± 7.3
SDI (%)	14 ± 5.2

Values are mean ± SD or n (%).
LBBB = left bundle branch block; LVD = left ventricular dysfunction; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association; SDI = systolic dyssynchrony index.

Compliance with guidelines for patient selection. Seventy (47.6%) patients did not fulfill strict implantation criteria. Of these patients, 24 (16.3%) had atrial fibrillation; 23 (15.6%) had QRSd <120 ms; and 9 (6.1%) had NYHA functional class II symptoms at the time of implant. Seventeen patients (11.6%) underwent upgrade of pacemaker to biventricular device (4 of whom also had atrial fibrillation). These groups are summarized in Figure 1.

Interhospital variability. The 62 datasets pooled from the 2 specialist centers (KCH and CUHK) were independently analyzed at both sites. Five (8.1%) were deemed to have poor image quality, of which analysis could not be completed in 4 cases (6.5%). Of the remainder, 48 (77.4%) had average image quality and 9 (14.5%) had excellent image quality.

There was excellent correlation between both centers for both LV end-diastolic volume (r = 0.95, mean difference: 4.61 ± 23.2 ml, 2.9% variability, ICC: 0.97), LVESV (r = 0.95, mean difference: 1 ± 19.6 ml, 1% variability, ICC: 0.98), and LVEF (r = 0.84, mean difference: 2 ± 4.9%, 7.1% variability, ICC: 0.91). There was also very good agreement in quantification of dyssynchrony with variability for SDI of 7.6% (r = 0.76, mean difference: 0.07 ± 3.38%, ICC: 0.84). Linear correlation and Bland-Altman plots demonstrate the excellent interhospital agreement (Fig. 2).

Outcomes from CRT. The overall clinical and echocardiographic outcomes were consistent with published findings. At the latest follow-up (mean 7 ± 3 months following implantation), 116 (78.9%) patients were reported as having subjective im-

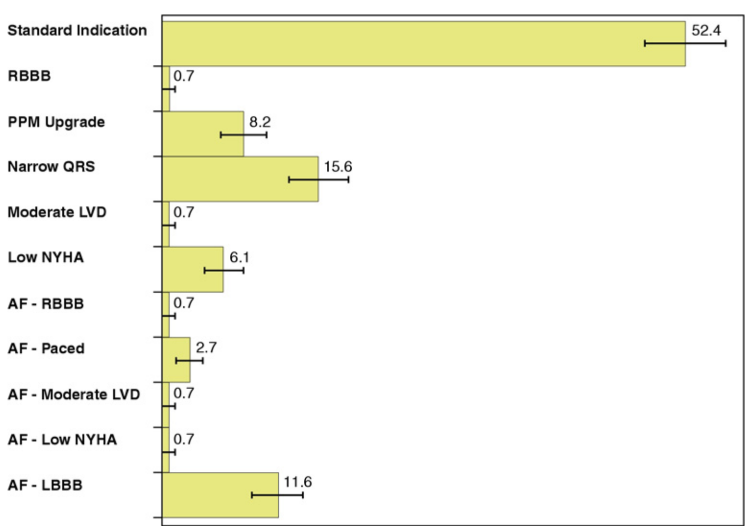

Figure 1. Histogram of Patients Fulfilling Standard Criteria

The histogram illustrates the proportion of patients fulfilling standard criteria. In patients not fulfilling standard criteria the proportion of each exception is shown (some groups overlap). AF-LBBB = proportion of patients in atrial fibrillation that would have otherwise fulfilled traditional implantation criteria; AF-Low NYHA = proportion of patients in atrial fibrillation with New York Heart Association functional class I or II; AF-Moderate LVD = proportion of patients in atrial fibrillation with left ventricular ejection fraction between 35% and 45%; AF-Paced = proportion of patients in atrial fibrillation with paced rhythm; Low NYHA = patients in New York Heart Association functional class I or II; Moderate LVD = left ventricular ejection fraction between 35% and 45%; Narrow QRS = QRS duration of <120 ms; PPM Upgrade = proportion of patients with paced rhythm. AF = atrial fibrillation; LBBB = left bundle branch block; LVD = left ventricular dysfunction; NYHA = New York Heart Association; PPM = permanent pacemaker; RBBB = right bundle branch block.

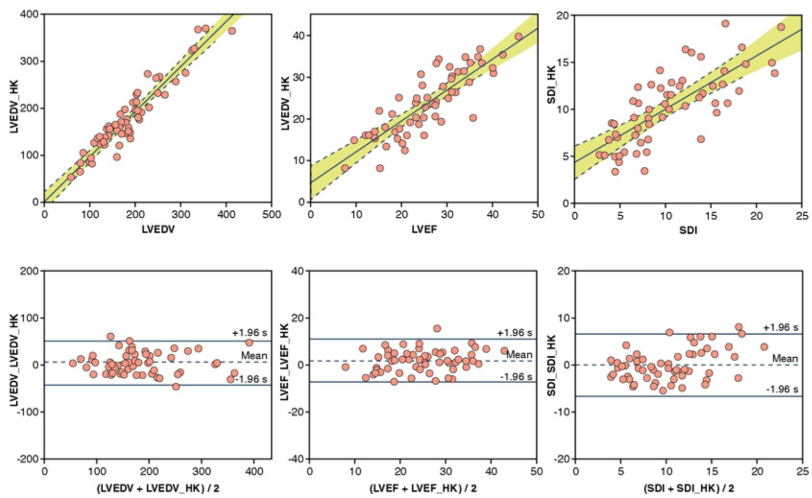

Figure 2. Interhospital Agreement for 3D Echo

Linear regression **(top row)** and Bland-Altman graphs **(bottom row)** demonstrating the agreement in quantification of 3-dimensional end-diastolic volume, left ventricular ejection fraction, and SDI between King's College Hospital, London, and Prince of Wales Hospital, Hong Kong. HK= Prince of Wales Hospital, Hong Kong; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; SDI = systolic dyssynchrony index; 3D= 3-dimensional.

provement with reduction in NYHA functional classification by at least 1 class. Ninety-six patients (65.3%) demonstrated a ≥20% relative increase in LVEF, but only 61 (41.6%) demonstrated a ≥15% reduction in LVESV. A smaller increase in LVEF was found to more closely reflect NYHA functional class changes: 123 (83.6%) of patients had a 10% relative increase in LVEF.

In patients with ≥20% improvement in LVEF, there was a highly significant reduction in SDI (ΔSDI: 5.9 ± 4.3%, $p < 0.0001$) and a similar reduction was also seen in patients with symptomatic improvement (mean ΔSDI: 5.9 ± 0.4%, $p < 0.0001$). In patients exhibiting reverse remodeling with reduction in LVESV, there was also a significant reduction in SDI (ΔSDI: 6.1 ± 0.66%, $p = 0.009$). There was a good correlation between change in LVEF and change in SDI (linear correlation coefficient: 0.62). There was good linear correlation between baseline SDI and increase in LVEF ($r = 0.55$, $p < 0.0001$), whereas the best correlation was found to be quadratic (polynomial fit degree = 2, $r = 0.67$, $p < 0.0001$), and from the scatter plot, it is obvious this is due to a plateau in ΔLVEF with increasing SDI (Fig. 3).

No significant difference in clinical or echocardiographic response was noted between male or female patients with or without ischemic heart disease (2-tail Fisher exact test $p > 0.1$ for all comparisons).

Predicting outcomes from CRT. Figures 4 and 5 compare QRSd and SDI as predictors of response according to 4 parameters: functional improvement (≥1 NYHA functional class), systolic function (≥20% relative improvement in LVEF), remodeling (≥15% improvement in LVESV), and ≥ 10% relative improvement in LVEF. Figure 4 shows scatter plots for QRSd and SDI according to response, and in Figure 5, ROC has been calculated for each predictor.

At baseline, QRSd was not significantly different between patients that had functional improvement and those that did not (QRSd: 137.5 ± 25.9 ms vs. 133.8 ± 25.9 ms, $p = 0.43$), whereas SDI was significantly different between groups at baseline (SDI: 15 ± 4.7 vs. 10.1 ± 5.1, respectively; $p < 0.0001$). This is reflected in the ROC curves, where the area under the curve (AUC) was 0.52 for QRSd and 0.79 for SDI. Based on ROC curves, the optimal cutoff for SDI in predicting response was 10.4%, which confers a sensitivity of 90% and a specificity of 67% for predicting reduction in NYHA functional classification by 1 class.

Echocardiographic improvement with ≥20% relative increase in LVEF was seen in 96 patients (29.2% nonresponder rate). Baseline QRSd was 139.5 ± 23.4 ms vs. 133.8 ± 22.8 ms for responders and nonresponders, respectively ($p = 0.19$). Between groups, SDI at baseline was significantly different (16.2 ± 4.7% vs. 10.6 ± 4.4%, respectively, $p < 0.0001$). In ROC analysis, the AUC for QRSd was 0.57, whereas it was significantly higher for SDI at 0.86. The optimum SDI cutoff for this outcome was 11.4%,

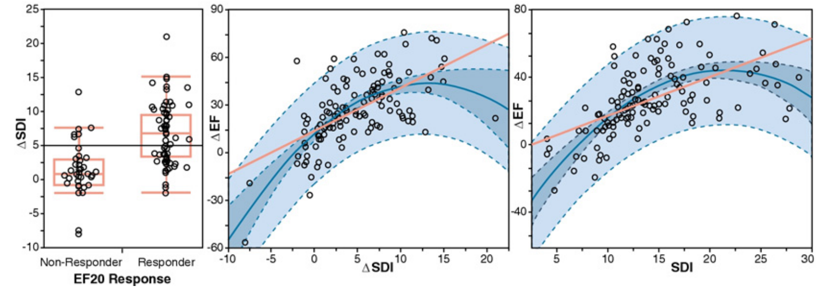

Figure 3. Change in SDI and LVEF After CRT

(A) Scatter plot illustrating the change in systolic dyssynchrony index in responders versus nonresponders (positive values for systolic dyssynchrony index difference denote reduction, $p < 0.001$). **(B)** Increase in left ventricular ejection fraction following cardiac resynchronization therapy correlates well with reduction in systolic dyssynchrony index. **(C)** Increase in left ventricular ejection fraction also correlates well with systolic dyssynchrony index. The **red line** illustrates linear correlation. The **blue line** illustrates polynomial correlation (best line fit) with **dark blue areas** showing confidence intervals for mean, line, and polynomial fits, and **lighter blue areas** showing the upper and lower 95% confidence limits for an individual predicted value, reflecting variation in the error and parameter estimates. CRT = cardiac resynchronization therapy; EF20 = 20% relative increase in ejection fraction; Δ = difference; other abbreviations as in Figure 2.

which has a sensitivity of 91% and specificity of 71% for predicting a significant increase in LVEF after CRT.

Only 41.6% of patients in our cohort demonstrated a ≥15% reduction in LVESV. Despite significant overlap, there was a statistically significant difference in baseline SDI but not QRSd between responders and nonresponders to this outcome ($p = 0.02$). AUC for QRSd was 0.57, versus 0.66 for SDI. The optimal SDI cutoff was 11.4%, conferring a sensitivity of 92% and specificity of 43%.

The greatest difference between responders and nonresponders was seen in the exploratory measure

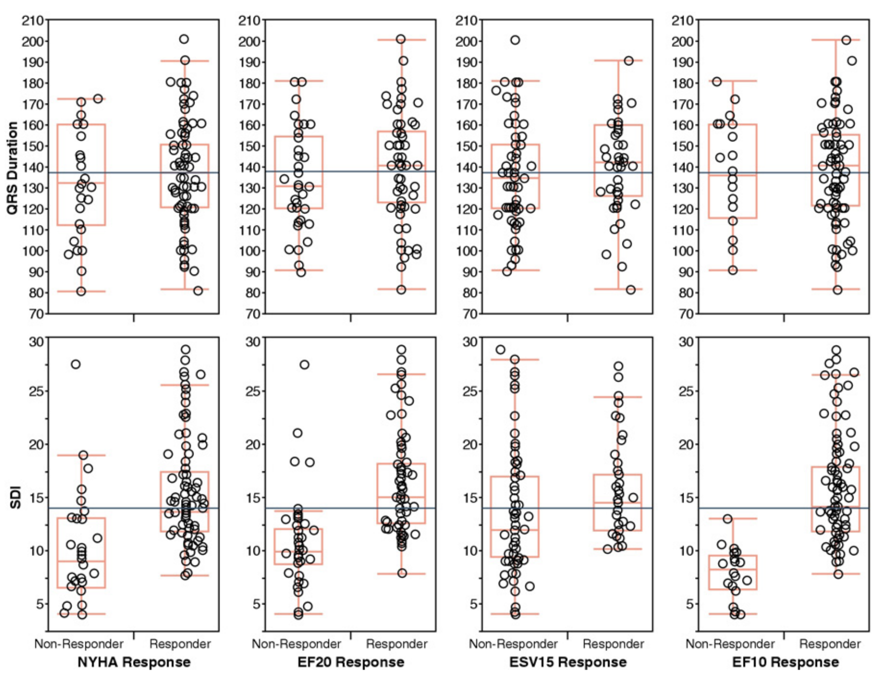

Figure 4. Baseline QRS Duration and SDI in Responders and Nonresponders

Scatter plots for QRS duration **(top row)** and systolic dyssynchrony index **(bottom row)** illustrating distribution in responders and nonresponders by New York Heart Association functional class, 20% relative increase in left ventricular ejection fraction, 15% reduction in left ventricular end-systolic volume, and 10% relative increase in left ventricular ejection fraction. In all comparisons, QRS duration did not differentiate between groups, whereas systolic dyssynchrony index was significantly higher in responders. EF10 = 10% relative increase in ejection fraction; ESV15 = 15% reduction in end-systolic volume; other abbreviations as in Figures 1, 2, and 3.

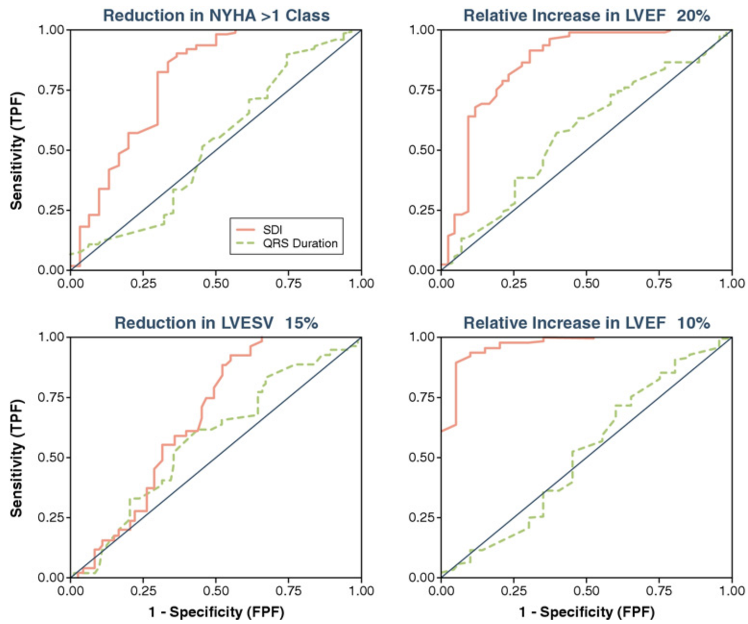

Figure 5. Predictive Value of Baseline QRS Duration and SDI in Outcomes After CRT

Receiver-operator characteristic curves for prediction of outcome by reduction in New York Heart Association functional class, 20% relative increase in left ventricular ejection fraction, 15% reduction in left ventricular end-systolic volume; and 10% relative increase in left ventricular ejection fraction. Systolic dyssynchrony index **(solid line)** performed significantly better in all comparisons, whereas QRS duration **(dotted line)** showed no predictive value with area under the curve of close to 0.5 for all comparisons. FPF = false positive fraction; LVESV = left ventricular end-systolic volume; TPF = true positive fraction; other abbreviations as in Figures 1, 2, and 3.

of outcome of a 10% relative increase in LVEF, which also appears to more closely correlate to NYHA response as the optimal SDI cutoff was similar (10.7%). Baseline QRSd was similar between groups ($p = 0.69$), whereas there was a significant difference in SDI (15.5 ± 4.8 vs. 7.9 ± 2.4% for responders and nonresponders, respectively, $p < 0.0001$) (Fig. 4). For SDI, AUC was 0.96, and the optimal cutoff of 10.7% conferred a sensitivity of 89% and specificity of 99% for this outcome.

Patients not conforming to traditional criteria. A small proportion of our cohort had persistent AF at implantation ($n = 19$), paced rhythm ($n = 17$), and/or QRSd <120 ms ($n = 33$). Although the study design does not allow definitive investigation of outcomes in these groups, we observed similar outcomes to those stated with respect to clinical echocardiographic and remodeling responses after CRT.

In patients with AF, we observed similar outcomes to patients with normal sinus rhythm. QRSd was similar in both responders and nonresponders in all outcomes ($p > 0.28$ for all comparisons), whereas SDI was significantly higher in responders by improvement in NYHA functional class and in LVEF ($p = 0.02$ and $p = 0.008$, respectively), but not by reduction in LVESV ($p = 0.3$).

In patients with paced rhythm undergoing CRT upgrade, QRSd was significantly higher (151.2 vs. 134.8 ms, $p = 0.006$), whereas baseline NYHA functional class, LV end-diastolic volume, LVEF, and SDI were similar to nonpaced subjects ($p > 0.7$ for all comparisons), although no paced patients had an SDI of less that 10.4%. The observed response rate was similar across all outcomes.

Baseline QRSd was not statistically different between any of these groups ($p > 0.22$). Baseline SDI was not significantly different in patients with and without remodeling ($p = 0.48$) and showed a trend to difference in those with clinical response ($p = 0.07$). However, there was a statistically significant difference between echo responders ($p = 0.009$).

Probabilistic nature of SDI. Using logistic regression and ROC curves for predicting a 20% relative increase in LVEF, the probability of a positive response was calculated for each level of QRSd and SDI and was plotted against these parameters (Fig. 6). For SDI, unit odds ratio was 0.236 and range odds ratio <0.0001. For QRSd, the unit odds ratio was 0.996 and range odds ratio was 0.599. Though the plot is nearly linear for QRS, illustrating that a wide of QRSd have the same probability, there is a sigmoid probability distribution for SDI. From this,

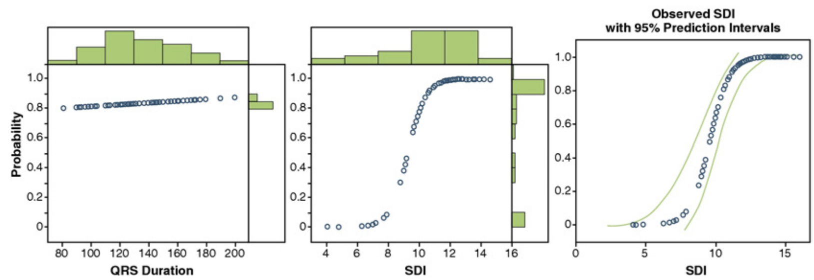

Figure 6. Probability of a Positive Response to CRT Predicted by QRS Duration and SDI Plotted Against These Variables

QRS duration **(A)** does not predict response, as probabilities are similar across the range of its values. Systolic dyssynchrony index **(B)** shows a sigmoid probability curve with values of <7.5% corresponding to very low chance of responding whereas values of >10.5% correspond to a very high probability; there is a "gray zone" between these values where small changes in systolic dyssynchrony index correspond to large changes in probability and is therefore less reliable. The histograms along each axis reflect the distribution of subjects. Using inverse prediction, the mean and 95% confidence limits for predicted systolic dyssynchrony index were estimated for each level of probability of positive response **(C)**. Abbreviations as in Figures 2 and 3.

it becomes apparent that above an SDI of 10.4%, there is a high probability of responding that does not increase significantly with higher SDI. Below 7.5%, there is a low probability of response, which does not reduce further with lower SDIs. Using SDI and QRSd as dichotomous variables with a cutoff of 10.4% and 120 ms, respectively, odds ratios for improvement in LVEF were 147 (27.47 to 786.67) and 0.62 (0.2 to 1.92), respectively.

How would 3D echo have influenced patient selection? Applying selection criteria retrospectively to this population, if only patients meeting traditional criteria (sinus rhythm and either QRSd >150 ms or QRSd ≥120 with echo evidence of dyssynchrony) were included, then this would have resulted in a higher response rate (88.3% functional improvement, 70.6% systolic function, and 47.1% remodeling) and excluding 47.6% of the cohort, of which 48 (68.6% of those not fulfilling these criteria), 34 (59.6%), and 20 (35.1%) would have responded by NYHA functional class, LVEF, and ESV, respectively.

Applying stricter ECG criteria to include only patients with sinus rhythm and QRSd ≥150 ms would have resulted in a similar response rate (80%, 75%, and 47.2%, respectively) at the cost of excluding 72.8% of the cohort, of which 84 (78.5% of those not fulfilling these criteria), 55 (61.8%), and 35 (39.3%) would have responded by NHYA functional class, LVEF, or ESV, respectively.

Subselection of this cohort using LVMD only (with an SDI ≥10.4%), and including patients with atrial fibrillation and all QRSd, would have resulted in a much higher response rate in all outcomes (90.3%, 81%, and 51%, respectively), and excluding only 28% of the cohort, of which 10 (34.8% of those not fulfilling this criterion) would have responded by NYHA functional class. No responders by LVEF or LVESV would have been excluded.

DISCUSSION

The current study investigates the value of SDI in the largest cohort so far of patients undergoing CRT to be investigated with RT3DE. The key findings of this study are: 1) 3D quantification of LV volumes, function, and LVMD is reproducible across centers; 2) in patients already selected for CRT, QRSd is not predictive of either clinical or echocardiographic outcomes, whereas SDI is highly predictive; 3) patients with atrial fibrillation or normal QRSd but with high SDI have comparable outcomes to those selected by traditional criteria; and 4) the occurrence of reverse LV remodeling, as described by a 15% reduction in LVESV, was much lower than anticipated based on published studies and did not reflect clinical improvement, suggesting that this may not be an adequate measure of outcome.

In keeping with previous reports, quantification of volumes and ejection fraction by 3D echo is accurate and highly reproducible, which is reflected in the very high interobserver agreement between centers in the current study. The large cohort selected for analysis had variable image quality reflecting real-life results. Fewer than 10% of cases had poor image quality and fewer than 15% had excellent image quality. 3D quantification of LV function would therefore appear preferable to other echocardiographic methods for serial clinical evaluation of individual patients as well as quantification of dyssynchrony.

In the current cohort of patients already selected for CRT, QRSd was found to have no further prognostic value, whereas SDI has highly accurate in separating responders from nonresponders for all outcomes. The best cutoff for SDI was found to be 10.4%, which confers sensitivity >90% and specificity of >67% for all outcomes after CRT. SDI provides a probabilistic assessment of outcome with very high probability of positive response at >10.4% and very low probability at SDI <7.5%.

A recent observational study comparing 16 patients with dilated cardiomyopathy and LBBB and 16 patients with dilated cardiomyopathy without LBBB to normal subjects found that all patients had SDI higher than that of normal subjects (4%) and that SDI was independent of QRSd (31), in keeping with our previous findings (13). The investigators concluded that the lack of differentiation between the 2 groups of heart failure patients proved SDI was not a useful discriminator of dyssynchrony. This study did not, however, examine clinical outcomes following CRT, and the cutoff for SDI used was the upper 95% confidence interval for normal subjects, which is a "normality" threshold, rather than a "response" threshold. Our current study demonstrates that it is not sufficient to have above-normal intraventricular dyssynchrony, but that a significantly higher SDI (10.4%) is associated with positive outcomes. A similar cutoff for SDI has also been found by Soliman et al. (29), where an SDI >10% was found to be highly predictive of positive outcome after CRT. Marsan et al. (24) identified a much lower cutoff (6.4%), but analyses were performed on a different software platform that applies a different segmentation model to the mathematical representation of the LV cavity, indicating that cutoffs are specific to the software platform used.

Approximately one-fifth of our cohort did not strictly conform to established selection criteria but a high SDI indicated a positive outcome following CRT in most cases in patients with pre-implantation paced rhythm, atrial fibrillation, or narrow QRS. Current evidence (32,33) suggests that even patients with low NYHA functional class may benefit, but numbers of such patients in our cohort were too low to assess.

Study limitations. Data in this study are retrospective and not powered for subgroup analysis, which will inevitably influence the accuracy of sensitivity and specificity, particularly in groups not fulfilling standard criteria for CRT implantation. It was not possible to obtain data from other modalities, such as tissue Doppler, for comparison, as these were not performed in a controlled manner in a large proportion of patients. Functional testing was not available for the majority of the patients. Applying "what if" scenarios retrospectively is limited by selection bias.

Presence, extent, and localization of myocardial scar tissue has been found to be potentially associated with reduction in LVESV following CRT (34–36). Although we found SDI to be a stronger predictor of this outcome after CRT than QRSd, its predictive value is significantly lower than for other outcomes and perhaps inclusion of scar information will strengthen this. During the study period, no patient underwent pre-implantation cardiac magnetic resonance imaging, and, therefore, it was not possible to correlate myocardial scar with 3D dyssynchrony and clinical outcomes from CRT. Similarly, pacing lead position was not recorded routinely and, therefore, could not be correlated to the extent of baseline dyssynchrony and clinical outcomes.

Data in this study were derived from 2 independent centers; however, large-scale prospective studies are needed to establish whether this highly promising technique can be translated to routine use for patient selection across the world.

CONCLUSIONS

Real-time 3D echo provides an accurate, reproducible quantification of LVMD. In patients selected for CRT, 3D SDI is a superior predictor of outcomes therapy compared with QRSd and has a role in further evaluating and monitoring patients undergoing this intervention and potentially has a role in patients not fulfilling traditional selection criteria.

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